

**Naval Health Research Center
Environmental Health Effects Laboratory**

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**DERIVATION OF EXPOSURE DURATION-SPECIFIC OCCUPATIONAL
EXPOSURE LIMITS (OELS) FOR 4,6-DIMETHYL-2-HEPTANONE
(CAS# 19549-80-5)**

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Abstract:

Occupational Exposure Limits (OELs) were calculated for 4,6-dimethyl-2-heptanone (CAS# 19549-80-5) using procedures established by the National Research Council (2001) for calculating Acute Exposure Guideline Levels. There were no appropriate toxicity data available for 4,6-dimethyl-2-heptanone to use in calculating OELs. 4,6-Dimethyl-2-heptanone is similar in chemical structure to 2,6-dimethyl-4-heptanone. The NOEL for 2,6-dimethyl-4-heptanone toxicity in rats of 125 ppm was used as a point of departure for estimating OELs for 4,6-dimethyl-2-heptanone. An total uncertainty factor of 300 was applied to the estimated NOEL to account for lack of toxicity information for 4,6-dimethyl-2-heptanone ($UF_1 = 10$), uncertainty associated with extrapolating to humans from animal study data ($UF_2 = 10$), and uncertainty of the existence of individuals within the population that may be very reactive to 4,6-dimethyl-2-heptanone exposure ($UF_3 = 3$). The calculated OELs for 4,6-dimethyl-2-heptanone ranged from 1.8 ppm for a 5-minute exposure to 0.36 ppm for a 480-minute exposure.

Background:

Naval Health Research Center/Toxicology was requested to provide an OEL for the chemical 4,6-dimethyl-2-heptanone. We searched TOXLINE, TOXNET, Hazardous Substances Databank, and the internet for information on the toxicity of 4,6-dimethyl-2-heptanone. However, we found no information on the toxicity of this compound. We located a Dutch MSDS sheet for 2-6-dimethyl-4-heptanone that indicates 4,6-dimethyl-2-heptanone is a contaminant of 2-6-dimethyl-4-heptanone. However, the MSDS sheet did not provide any information on the toxicity of 4,6-dimethyl-2-heptanone. Mr. Crawl (NEHC) found similar information in the Aldrich catalog indicating that 4,6-dimethyl-2-heptanone is a contaminant of 2-6-dimethyl-4-heptanone.

The chemical 2-6-dimethyl-4-heptanone is very similar in chemical structure to 4,6-dimethyl-2-heptanone. There is some data on the toxicity of 2-6-dimethyl-4-heptanone in rodents and humans. Since there is an absence of toxicity data for 4,6-dimethyl-2-heptanone, it is necessary to assume that this compound is at least as toxic as 2-6-dimethyl-4-heptanone based on similarities in chemical structure. Therefore, we derived OELs for 4,6-dimethyl-2-heptanone using published toxicity data for 2-6-dimethyl-4-heptanone. The rationale for the OELs that we derived for 4,6-dimethyl-2-heptanone is organized into 3 sections. The key study that provides the point of departure for calculating OELs for 4,6-dimethyl-2-heptanone is summarized in the Key Study section. Secondary studies supporting use of the selected key study for deriving OELs for 4,6-dimethyl-2-heptanone are summarized in the Other Studies section. The procedure used to calculate OELs for 4,6-dimethyl-2-heptanone is detailed in Calculation of Exposure Duration-Specific OELs for 4,6-Dimethyl-2-Heptanone.

Key Study: Carpenter et al. (1953) exposed rats seven hours at a time for a total of 30 exposure periods to 2-6-dimethyl-4-heptanone at atmospheric concentrations ranging from 125 ppm-1,650 ppm. An increase in mortality occurred in rats exposed repeatedly to 2-6-dimethyl-4-heptanone vapors, seven hours per exposure, at a concentration of 1,650 ppm. Repeat exposure of rats to 2-6-dimethyl-4-heptanone at 530 or 920 ppm resulted in increased liver and kidney weights. Repeat exposure to 2-6-dimethyl-4-heptanone at a concentration of 125 ppm resulted in no detectable toxicity and would be considered the only experimentally-determined No Observed Effect Level (NOEL) for 2-6-dimethyl-4-heptanone for toxic effects other than death.

Other Studies: A single 8-hour exposure to 2-6-dimethyl-4-heptanone at an atmospheric concentration of 2,000 ppm caused the death of 5 of 6 rats (Smyth et al. 1949). Neither the LC50 nor the threshold for lethality was determined in this experiment. No deaths were reported for guinea pigs and rats exposed to 2-6-dimethyl-4-heptanone at saturated vapor concentrations (approximately 3,200 ppm) for up to 16 hours (McOmie and Anderson 1949). Two human response studies have been conducted for 2-6-dimethyl-4-heptanone. A single 3-hour exposure to 2-6-dimethyl-4-heptanone at a concentration of 100 ppm caused slight irritation to the eyes, nose, and throat. A single 3-hour exposure to 50 ppm 2-6-dimethyl-4-heptanone was considered "satisfactory" (Carpenter et al. 1953). A second study found that the majority of 12 volunteers reported unpleasant odor and displayed some degree of eye irritation when exposed to 2-6-dimethyl-4-heptanone at concentrations above 25 ppm (Silverman et al. 1946).

Calculation of Exposure Duration-Specific OELs for 4,6-Dimethyl-2-Heptanone

Exposure duration-specific OELs for 4,6-dimethyl-2-heptanone were calculated according to guidelines set forth for calculating Acute Exposure Guideline Levels (AEGLs) by the National Research Council (NRC 2001). The NOEL of 125 ppm for an exposure duration of 7 hours (420 minutes) was used as the point of departure for estimating AEGLs for shorter exposure durations. A total uncertainty factor of 300 was applied to the 2,6-dimethyl-4-heptanone NOEL concentration of 125 ppm. An uncertainty factor of 10 was applied to the NOEL to account for the uncertainty associated with extrapolating animal study results to humans. A second uncertainty factor of 3 was applied to the NOEL to provide protection against toxicity among individuals in the human population that could be particularly sensitive to this chemical based on individual genetic, physical, nutritional or other individual-specific factor(s). A third uncertainty factor of 10 was applied to the NOEL to account for the fact that the NOEL for 4,6-dimethyl-2-heptanone is being derived from toxicity data for 2,6-dimethyl-4-heptanone.

OELs for 30, 60, 90, 120, and 240 minutes were derived from the 420 minute NOEL for 2,6-dimethyl-4-heptanone using the equation $C^n \cdot t = k$ where C is the derived NOEL (e.g., NOEL multiplied by the uncertainty factor of 300), t is the NOEL exposure duration, and $n = 3$ as recommended by NRC (2001) for extrapolating NOEL concentrations for durations shorter than the experimental NOEL. An $n=1$ was used to extrapolating NOEL concentrations for a duration of 480 minutes as recommended by NRC (2001). Given that the 7 hour NOEL for 2,6-dimethyl-4-heptanone is 125 ppm, the constant k would be calculated using the following equation:

$$C^n \cdot t = k$$

$$k = [125/300]^3 \text{ ppm} \cdot 420 \text{ minutes}$$

$$k = 30.38 \text{ ppm} \cdot \text{minutes}$$

Thus, the 5 minute OEL for 4,6-dimethyl-2-heptanone is 1.8 ppm. OELs calculated for exposure durations of 15, 30, 60, 90, 120, 240, and 480 minutes are listed in Table 1.

Table 1: OELs calculated for 4,6-dimethyl-2-heptanone based on NOEL toxicity data for 2,6-dimethyl-4-heptanone	
Exposure duration (minutes)	Recommended OEL (ppm)
5	1.8
15	1.3
30	1.0
60	0.80
90	0.70
120	0.63
240	0.50
480	0.36

Summary:

There is no available information on the toxicity of 4,6-dimethyl-2-heptanone (CAS# 19549-80-5). 4,6-Dimethyl-2-heptanone is similar in chemical structure to 2-6-dimethyl-4-heptanone. There is limited toxicity information available for 2-6-dimethyl-4-heptanone. Single exposures to 2-6-dimethyl-4-heptanone at 25 ppm and below did not cause objectionable irritation of the eyes and mucous membranes in human volunteers. However, no other endpoints of toxicity were evaluated in these studies. Repeat exposure to atmospheric concentrations of 125 ppm 2-6-dimethyl-4-heptanone did not produce a measurable toxic response in rats, whereas increased liver and kidney weights were identified in rats exposed to 530 ppm. The NOEL for 2-6-dimethyl-4-heptanone of 125 ppm was used as a point of departure for estimating OELs for 4,6-dimethyl-2-heptanone. OELs were calculated using procedures established by NRC (2001) for calculating Acute Exposure Guideline Levels. An total uncertainty factor of 300 was applied to the estimated NOEL to account for lack of toxicity information for 4,6-dimethyl-2-heptanone ($UF_1 = 10$), uncertainty associated with extrapolating to humans from animal study data ($UF_2 = 10$), and uncertainty of the existence of individuals within the population that may be very reactive to 4,6-dimethyl-2-heptanone exposure ($UF_3 = 3$). The calculated OELs for 4,6-dimethyl-2-heptanone ranged from 1.8 ppm for a 5-minute exposure to 0.36 ppm for a 480-minute exposure.

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